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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,707	12/21/2005	Aldo Olivieri	39330	8179

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EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,707	OLIVIERI ET AL.	
	Examiner	Art Unit	
	Ernst V. Arnold	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 17-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 21 December 2005 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3/20/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 have been cancelled. Claims 17-33 are pending and under examination.

Comment: Please insert the continuity data at the top of page 1.

Comment: Applicant has filed drawings on 12/21/05 but there is no Brief Description of the Drawings in the specification. Please correct.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 23 and 24 recite "scarcely soluble substances". It is unclear to the Examiner the metes and bounds of the subjective term "scarcely". The Examiner will interpret the claims as they read on any active substance.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites "low dissolution speed". It is unclear to the Examiner the metes and bound of the subjective term "low". Furthermore, it is unclear what the "scarcely water soluble substances" are dissolving in. The Examiner will interpret the claims as they read on any active substance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17- 28 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Breitenbach et al. (US 6,318,650) as evidenced by BASF technical information Kollidon VA 64 March 2000 pages 2-10.

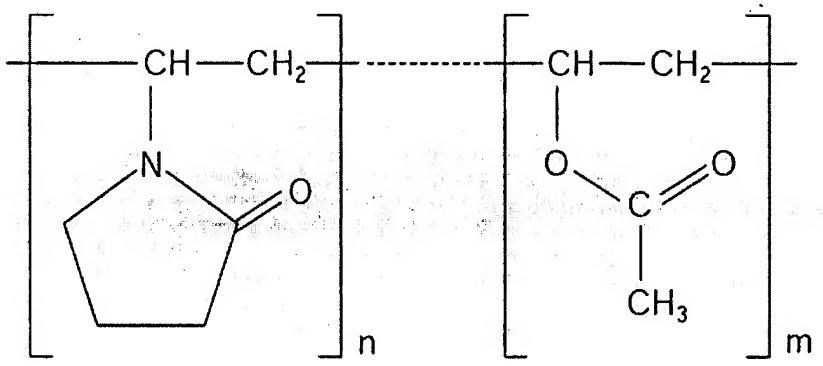
Breitenback et al. disclose in claim 1:

> 1. A process for the continuous production of solid, particulate preparations of bioactive substances, in which the bioactive substances are homogeneously dispersed in a matrix of thermoplastic auxiliaries, in a screw extruder having an extruder jacket, which extruder is divided into a plurality of zones, wherein the process comprises
>
> firstly melting the matrix auxiliaries and mixing the bioactive components with the matrix auxiliaries in a heatable zone of the extruder to form a mixture, and
>
> subsequently cooling, precomminuting and finely grinding the mixture in a cooling zone of the extruder to form a powder,
>
> wherein the screw geometry in the cooling zone is selected so that the cooling zone has a conveying zone as first zone, followed by a mixing zone and/or a kneading zone.

Breitenbach et al. specifically disclose in example 9 (column 10, lines 60-67 and column 11, lines 1-9) the use of Kollidon VA 64 as the matrix and ketoprofen as the

bioactive substance and the process produces a granule of 0.1 mm average particle size. From the technical information sheet on page 4, Kollidon VA 64 is:

> Kollidon VA 64 is a vinylpyrrolidone-vinyl acetate copolymer that is soluble both in water and in alcohols. It is used in the pharmaceutical industry as a binder in tablets, as a granulating agent, as a retarding agent and as a film-forming agent.
>
> It is available from BASF as Product No. 95405-2-43.
>
> For further details that are beyond the scope of this leaflet, please consult the book, "Kollidon – Polyvinylpyrrolidone for the Pharmaceutical Industry" 4th edition 1999 (BASF No. B 390 e).
>
> Copolyvidone; Copovidone; VP/VAc copolymer 60/40; copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 6 : 4 by mass.



$(C_6H_9NO)_n \times (C_4H_6O_2)_m$

$M_r = (111.1)_n \times (86.1)_m$

$n \approx 1.2\ m$

The particle size distribution on page 6 is:

2.7 Particle size distribution	The following values were determined with an air-jet sieve and should be regarded as typical values.	
	Finer than 50 µm	approx. 15 %
	Coarser than 250 µm	approx. 1 – 2 %

It is the Examiner's position that the Kollidon VA 64 and ketoprofen are simultaneously powders during the grinding process and reads on instant claims 17-20, 27-28 and 31.

With respect to the bioactive substances, Breitenbach et al. disclose a wide variety of substances in column 5, line 12 to column 6, line 32; such as:

antiinfectives aciclovir, aminoglycosides, amphotericin B, azole antimycotics, clotrimazole, itraconazole, sepraconazole, clindamycin, cephalosporins, chloramphenicol, erythromycin, 5-fluorouracil, etoposide, flucytosine, ganciclovir, griseofulvin, gyrase inhibitors, isoniazid, lincosamides, mebendazole, mefloquine, metronidazole, nitroimidazoles, novobiocin, platinum compounds, polymyxin B, praziquantel, pyrimethamine, rifamipicin, saquinavir, streptomycin, sulfonamides, tetracyclines, trimethoprim, vancomycin, zidovudine;

antipyretics, analgesics, antiinflammatory agents, paracetamol, ibuprofen, ketoprofen, oxaprozin, acetylsalicylic acid, morphine, propoxyphene, phenylbutazone;

antibiotics rifampicin, griseofulvin, chloramphenicol, cycloserine, erythromycin, penicillins such as penicillin G, streptomycin, tetracycline;

antiepileptics hydantoins, carbamazepine;

antitussives and antiasthmatics diphenhydramine;

antirheumatics chloroquine, indomethacin, gold compounds, phenylbutazone, oxyphenbutazone, penicillamine;

hypnotics barbiturates, phenobarbital, zolpidem, dioxopiperidines, ureides;

insecticides aldrin, dieldrin, chlorophenothane, hexachlorocyclohexane;

herbicides vinclozolin, strobilurins;

psychopharmaceuticals, neuroleptics perazine, promazine, sulpiride, thioridazine, chlorpromazine, meprobamate, triflupromazine, melperone, clozapine, risperidone, reserpine;

tranquilizers;

antidepressants imipramine, paroxetine, viloxazine, moclobemide;

psychostimulants;

psychomimetics;

diuretics potassium canrenoate, loop diuretics, furosemide, hydrochlorothiazide, spironolactone, thiazides, triamterene;

hormones androgens, antiandrogens, gestagens, glucocorticoids, estrogens, cortisol, dexamethasone, prednisolone, testosterone, Adiuretin, oxytocin, somatropin, insulin;

immunosuppressants ciclosporin;

bronchodilators;

muscle relaxants, tranquilizers carisoprodol, tetrazepam, diazepam, chlordiazepoxide;

enzymes lipase, phytase;

antigout agents allopurinol, colchicine;

anticoagulants coumarins;

antiepileptics phenytoin, phenobarbital, primidone, valproic acid, carbamazepine;

antihistamines chlorphenoxamine, dimenhydrinate;
antimimetics;
antihypertensives, antiarrhythmics lidocaine, procainamide, quinidine, calcium anatagonists, glycerol trinitrate, isosorbide dinitrate, isosorbide 5-mononitrate, pentaerythrityl tetranitrate, nifedipine, diltiazem, felodipine, verapamil, reserpine, minoxidil, captopril, enalapril, lisinopril;
sympathomimetics norfenefrine, oxedrine, midodrine, phenylephrine, isoprenaline, salbutamol, clenbuterol, ephedrine, tyramine, β-blockers such as alprenolol, metoprolol, bisoprolol;
antidiabetics biguanides, sulfonylureas, carbutamide, tolbutamide, glibenclamide, metformin, acarbose, troglitazone;
iron preparations;
vitamins vitamin C, B, A, D, folic acid;
ACE inhibitors captopril, ramipril, enalapril;
anabolic agents;
iodine compounds;
X-ray contrast agents;
CNS-active compounds;
antiparkinson agents biperiden, benzatropine, amantadine, opioid analgesics, barbiturates, benzodiazepines, disulfiram, lithium salts, theophylline, valproate, neuroleptics;
cytostatics;
antispasmolytics;
vasodilators naftidrofuryl, pentoxifylline.

As can be seen, anti-infectives, NSAIDs and analgesics such as ibuprofen, anti-hypertensives, hepato-biliary agents and poorly water soluble compounds such as the antibiotic amphotericin are all disclosed by Breitenbach et al. thus anticipating instant claims 20-26.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17- 19, 27-29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Roser et al. (US 5,958,455) as evidenced by BASF technical information Kollidon VA 64 March 2000 pages 2-10.

The BASF technical information sheet is discussed in detail above and that discussion is hereby incorporated by reference.

Roser et al. disclose in column 15, Example 3:

EXAMPLE 3

Use of AAT for Making Tablets Containing Active Agent: Stability Enhancement Over Use of Crystalline TD

Pre-formulated powders, containing AAT and a synthetic vasoactive peptide, together with binders and lubricants such as Kollidon VA64 (BASF), Citric acid (BDH), Aerosil 200 (Degussa), Magnesium stearate (BDH), Sodium lauryl sulfate (BDH), Polyethylene glycol 8000 (BDH), Glyceryl monostearate (Akzo Nobel) and Lutrol F68 (BASF) were blended using a Braun coffee grinder for a few seconds, before being sieved through a 30 mesh (500 micron) screen. Tableting was performed on a Manesty F3 single station, direct compression press. The speed was set at about 60–70 tablets per minute and compression was approximately 1–1.5 tons. The flow of the blend was controlled to give the desired weight distribution of the tablets produced.

It is the Examiner's position that a premixed powder composition of active substance and N-vinyl-2-pyrrolidone/vinyl acetate copolymer was ground in a coffee grinder resulting in particles less than 500 microns thus reading on instant claims 17-19, 27-29 and 31.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roser et al. (US 5,958,455) in view of BASF technical information Kollidon VA 64 March 2000 pages 2-10 and Kolter et al. (Drug Development and Industrial Pharmacy 2000, 26(11), 1159-1165) and with respect to claims 32 and 33 Czekai et al. (US 5,862,999).

Applicant claims a method for preparing a composite product comprising a step in which an active substance in powder form undergoes co-grinding with a carrier comprising N-vinyl-2-pyrrolidone/vinyl acetate copolymer in powder form.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Roser et al. teach in claims 1-6:

1. A method of making tablets comprising the steps of:

(a) combining components comprising an amount of anhydrous trehalose sufficient to act as an effective diluent in the tablets formed and an amount of an active agent such that each tablet formed contains an effective amount of active agent and an amount of aqueous solvent sufficient to suspend or dissolve the anhydrous trehalose and active agent;

(b) processing the product of step (a) to form a powder comprising a substantially homogeneous mixture of the components, wherein the powder is formed using a process other than spray freeze drying; and

(c) forming tablets from the powder.

2. The method according to claim 1, wherein the components of step a) further comprise at least one excipient.

3. The method according to claim 1, further comprising the steps of b1) adding excipients to the powder; and b2) mixing the excipients and powder to form a substantially homogeneous mixture.

4. The method according to claim 1 or 2, wherein the excipient is selected from the group consisting of diluents, binders, lubricants, disintegrants, coloring agents and flavoring agents.

5. The method according to claim 4, wherein the diluent is selected from the group consisting of trehalose, dicalcium phosphate, dihydrate, calcium, tricalcium phosphate, sulfate, lactose, spray-dried lactose, pregelatinized starch, microcrystalline cellulose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar.

6. The method according to claim 4, wherein the binder is selected from the group consisting of starch, gelatin, sugars, natural and synthetic gums, Ludipress, Kollidon, polyvinyl pyrrolidone and hydroxyethyl starch.

Roser et al. teach dry mixing and grinding as a common method of forming powders in

column 9, lines 19-27.

> then used to produce the dry powder formulation. This incorporates the active agent directly in the tablet without the need for subsequent processing prior to tableting to combine the dry active agent and binder. The various components can, of course, be combined in the dry form and mixed by any method known in the art such as milling, granulating, blending and grinding. This is the most common method of forming powders for tableting and is suitable for use where homogeneity at a molecular level is not required.

Roser et al. teach Kollidon VA 64 as the binder (column 10, lines 65-67).

Roser et al. teach that the active agent can be any known in the tabletting art and is typically a pharmaceutical agent (column 11, lines 25-67 and claim 20).

The BASF technical sheet on Kollidon VA 64 is discussed in detail above and that discussion is hereby incorporated by reference.

Kolter et al. teach Kollidon VA 64 has binding properties that far exceed those of other binders and that Kolldion VA 64 allows for the manufacture of tablets with outstanding mechanical properties (Page 1165, conclusion).

Czekai et al. teach methods of grinding pharmaceutical substances (Abstract and claims 1-26). Czekai et al. teach in column 3, lines 30-39:

> Grinding can take place in any suitable grinding mill. Suitable mills include an airjet mill, a roller mill, a ball mill, an attritor mill, a vibratory mill, a planetary mill, a sand mill and a bead mill. A high energy media mill is preferred especially when the grinding media is a polymeric resin. The mill can contain a rotating shaft. This invention can also be practiced in conjunction with high speed dispersers such as a Cowles disperser, rotor-stator mixers, or other conventional mixers which can deliver high fluid velocity and high shear.

And in column 3, lines 57-64:

> The attrition time can vary widely and depends primarily upon the particular therapeutic or diagnostic agent, mechanical means and residence conditions selected, the initial and desired final particle size and so forth. For roller mills, processing times from several days to weeks may be required. On the other hand, residence times of less than about 8 hours are generally required using high energy dispersers and/or media mills.

Czekai et al. thus establish a wide variety of means to achieve grinding in the art as well as various processing times.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Roser et al. is that Roser et al. do not expressly teach a method of co-grinding NSAIDs, anti-hypertensives, hepato-biliary agents, substances that are scarcely soluble in water and substances that have low dissolution speed with N-vinyl-2-pyrrolidone/vinyl acetate copolymer.

2. The difference between the instant application and Roser et al. is that Roser et al. do not expressly teach a method of co-grinding where the active substance and copolymer are introduced into the grinding mill without premixing.

3. The difference between the instant application and Roser et al. is that Roser et al. do not expressly teach a method of co-grinding where the co-grinding is carried out at low or high energy for times varying from 0.1 to 48 hours or the narrower range of 0.5 to 8 hours. This deficiency in Roser et al. is cured by the teachings of Czekai et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to co-grind NSAIDs, anti-hypertensives, hepato-biliary agents, substances that are scarcely soluble in water and substances that have low dissolution speed and any of the pharmaceutical agents listed in claims 25 and 26 with N-vinyl-2-pyrrolidone/vinyl acetate copolymer, as suggested by Roser et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Roser et al. teaches that any pharmaceutical agent, which would encompass those in claims 20-26, can be used and co-ground with Kollidon VA 64.

The Examiner notes that is appears as if Applicant has 'discovered' certain technical properties of the N-vinyl-2-pyrrolidone/vinyl acetate copolymer such as: "The

formation of inter-particle bonds enables to obtain a tablet pharmaceutical form having a higher hardness than the one that could be obtained with other traditional excipients..." (specification page 6, line 33 to page 7, line 2). However, such an increase in hardness is already known in the art as taught by Kolter et al. (pag– 1164, Table 8). Indeed, Kolter et al. teach that Kollidon VA 64 produces the steepest increase in hardness (page 1164, top right column). The art has thus established the beneficial properties of using Kollidon VA 64 in tablet composition.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to co-grind where the active substance and copolymer are introduced into the grinding mill without premixing and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because the end result remains the same; a ground powdered sample is obtained. Selection of any order of mixing ingredient is prima facie obvious in the absence of new or unexpected results (see, e.g., In re Gibson, 5 USPQ 230 - CCPA 1930) - MPEP 2144.04.)

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to co-grind where the co-grinding is carried out at low or high energy for times varying from 0.1 to 48 hours or the narrower range of 0.5 to 8 hours.

One of ordinary skill in the art would have been motivated to do this because it is merely routine optimization of the grinding method selected, as taught by Czekai et al., to arrive at the instantly claimed times.

Summary: The art teaches grinding pharmaceutical formulations. The art teaches various means of grinding. The art teaches that the copolymer of N-vinyl-2-pyrrolidone/vinyl acetate is the best binder. One of ordinary skill in the art would desire the best binding agent in their drug formulation and co-grind the drug with N-vinyl-2-pyrrolidone/vinyl acetate copolymer with the expected result of producing the best composite product. From recent case law: "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." (KSR INTERNATIONAL CO. v. TELEFLEX INC. ET AL.. 550 U. S. ____ (2007) page 24).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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